DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

SEP 8 2005

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James Demas
Winston Laboratories, Inc.
100 Fairway Drive, Suite 134
Vernon Hills, IL 60061

Re: Docket No. 2004P-0265/CP1

Dear Mr. Demas:

This letter responds to your citizen petition dated May 24, 2004 (Petition), filed on behalf of Winston Laboratories, Inc. (Winston). You request that the Food and Drug Administration (FDA) designate an official name for cis-8-methyl-N-vanillyl-6-nonenamide (the compound) different from the current official United States Adopted Name (USAN) for the compound. FDA has considered the information submitted in your petition and addresses your request in this response. For the reasons explained below, your petition is denied.

I. BACKGROUND

A. USAN Council's role in naming drugs

The United States Adopted Names Council (USAN Council) is a private organization sponsored by the American Medical Association, the American Pharmaceutical Association, and the U.S. Pharmacopeia (USP), that selects nonproprietary names for drugs. The principal function of a nonproprietary name is to identify the substance to which it applies and to serve as a designation that may be used without restriction by the public (as distinguished from trademarked names that have been registered for private use). All three sponsoring organizations are represented on the USAN Council. In addition, an FDA liaison representative sits as a voting member of the USAN Council. The USAN Council chooses each nonproprietary name for a drug product following a set of established principles developed to ensure safety, consistency, and logic in the choice of names. These principles are published in the USAN and the USP Dictionary of Drug Names (USP Dictionary) as *Guiding Principles for Coining U.S. Adopted Names for Drugs* (guiding principles), and consist of both general and specific rules.

The USAN Council enlists the cooperation of the pharmaceutical industry in the United States as well as nomenclature groups abroad to select a single nonproprietary name for each new drug. The USAN Council works with the World Health Organization (WHO), which is responsible for coordinating existing nomenclature at the international level through its Committee on Nonproprietary Names. WHO selects International

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Nonproprietary Names (INNs) and proposes or recommends to its member states that such names be adopted at the local level.

Any disputes that arise as a result of decisions made by the USAN Council may be appealed to the USAN Review Board. The USAN Review Board is the final arbitrator of nomenclature disputes between the USAN Council and drug manufacturers.

B. FDA's role in naming drugs

Under section 508 of the Federal Food, Drug, and Cosmetic Act (the Act), the Secretary of Health and Human Services is authorized to designate an official name for any drug whenever deemed "necessary or desirable in the interest of usefulness and simplicity" (21 U.S.C. 358). Section 299.4 of FDA's regulations, which implements section 508 of the Act, states, in part:

> (c) The Food and Drug Administration recognizes the skill and experience of the U.S. Adopted Names Council (USAN) in deriving names for drugs. . . .
>
> (d) The Food and Drug Administration cooperates with and is represented on the USAN Council. In addition, the Food and Drug Administration agrees with "Guiding Principles for Coining U.S. Adopted Names for Drugs," published in *USAN and the USP Dictionary of Drug Names*. . . . All applicants for new-drug applications and sponsors for "Investigational New Drug Applications" (INDs) are encouraged to contact the USAN Council for assistance in selection of a simple and useful name for a new chemical entity. . . . Prior use of a name in the medical literature or otherwise will not commit the Food and Drug Administration to adopting such terminology as official.
>
> (e) The Food and Drug Administration will not routinely designate official names under section 508 of the act. As a result, the established name under section 502(e) of the act will ordinarily be either the compendial name of the drug or, if there is no compendial name, the common and usual name of the drug. Interested persons, in the absence of the designation by the Food and Drug Administration of an official name, may rely on as the established name for any drug the current compendial name or the USAN adopted name listed in *USAN and the USP Dictionary of Drug Names*. The Food and Drug Administration, however, will continue to publish official names under the provisions of section 508 of the act when the agency determines that:
>
> > (1) The USAN or other official or common or usual name is unduly complex or is not useful for any other reason;
> >
> > (2) Two or more official names have been applied to a single drug, or to two or more drugs that are identical in chemical structure and

> pharmacological action and that are substantially identical in strength, quality, and purity; or
>
> (3) No USAN or other official or common or usual name has been applied to a medically useful drug. . . .

The established name of a drug is defined in section 502(e) of the Act as (1) an official name designated pursuant to section 508 of the Act or (2) if no such official name has been designated for the drug and the drug is an article recognized in an official compendium, then the official title thereof in such compendium; and (3) if neither paragraph (1) or (2) applies, then the common or usual name of the drug. To avoid misbranding, a drug product's labeling must bear its established name, if there is one, to the exclusion of any other nonproprietary name (except the applicable systematic chemical name or the chemical formula) and, if the drug is fabricated from two or more ingredients, the established name of each active ingredient (21 USC 352(e)).

C. Zucapsaicin

The USAN Council adopted the name zucapsaicin for the compound on November 23, 1993, after negotiation with GenDerm Corporation (the previous sponsor). GenDerm accepted this name in a letter to the USAN Council dated July 13, 1993 (Petition at Appendix 11). The name zucapsaicin was approved by the World Health Organization International Nonproprietary Name Committee in INN List 71 (WHO Drug Information, Vol. 8, No. 2, 1994). The name zucapsaicin was republished as the recommended INN in List 35 (WHO Drug Information, Vol. 9, No. 3, 1995) and is the recommended nonproprietary name for use in all WHO member countries. Zucapsaicin has been included in the USP Dictionary since 1994.

After acquiring the rights to zucapsaicin in 1999, you petitioned the USAN Council requesting a name change for the compound from zucapsaicin to civamide. Your request was denied by the USAN Council in July 2000 and then the USAN Council reconsidered your request and on September 10, 2001 informed you that it chose to support retaining the name zucapsaicin. You then filed a complaint against the USAN Council in the Circuit Court of Cook County, Illinois County Department, Chancery Division, on April 15, 2002. Your complaint was dismissed on November 8, 2002. On March 17, 2003, you appealed the earlier USAN Council decision to the USAN Review Board. On December 19, 2003, the USAN Review Board denied your appeal and upheld the decision of the USAN Council to retain the name zucapsaicin for the compound.

II. DISCUSSION

You now petition FDA to designate an official name for the compound, stating that the name zucapsaicin is an inappropriate nonproprietary name for the compound and violates

several fundamental guiding principles (Petition at 2-3).[1] You also state that the name zucapsaicin unnecessarily exposes patients, physicians, pharmacists, health care and scientific professionals, and your company to various types of risk and, therefore, has potential to cause harm (Petition at 4). You also request that FDA notify WHO of any new official name in order to change the INN of the compound. If this is not possible, you state that the benefit from changing the name of the compound outweighs the inconsistencies between a new official name and the existing INN (Petition at 3). We address your arguments below.

A. Guiding principles for nonproprietary drug names

You state that the name zucapsaicin violates several of USAN's guiding principles, including:

> • General Rule 4: A name should be free from conflict with other nonproprietary names and with established trademarks and should be neither confusing nor chemically misleading. . . .
>
> • General Rule 5: Preference should be given to names of established usage provided they conform to these guiding principles and are determined to be free from conflict with existing nonproprietary names and trademarks.
>
> • Specific Rule 14: A name coined for a new chemical entity routinely does not specify the stereoisomeric form of the molecule in the nonproprietary name. If the stereochemical configuration has been determined, this information is presented in the chemical name(s) and is reflected in the structural formula. . . . (Petition at 4.)

You request that FDA change the official name to civamide or some other name not containing capsaicin (Petition at 3).

The USAN Review Board was established to resolve disputes between the USAN Council and drug manufacturers and has expertise in interpreting USAN's guiding principles. The USAN Review Board has addressed the issues you raise. We have reviewed their determinations and agree that the name zucapsaicin does not violate the above guiding principles.

Moreover, FDA does not believe that your arguments establish a basis to determine that the USAN is unduly complex or not useful (21 CFR 299.4(e)(1)). As explained further below, the name zucapsaicin identifies the compound as a geometric isomer of capsaicin. The name is inherently useful as it informs health care practitioners that the compound differs from capsaicin in stereochemistry. Also, the simplicity of adding the two-letter

[1] While your petition does not specify the specific regulatory provision under which you are requesting FDA to designate an official name, we presume that the basis for your request would be 21 CFR 299.4(e)(1).

prefix "zu" to the stem "capsaicin" to make this distinction demonstrates that the name zucapsaicin is not unduly complex. As explained below, your arguments and evidence fail to show that the USAN is unduly complex or not useful. Therefore, we find that the name zucapsaicin is neither "unduly complex" nor "not useful" under 21 CFR 299.4(e)(1), and we decline to designate an official name under section 508 of the Act.

1. General Rule 4

You state that the name zucapsaicin is similar to capsaicin, the name of the active constituent in several marketed drugs and a term that is already surrounded by considerable confusion as to whether it encompasses synthetic capsaicin, capsaicinoids, and/or capsaicin oleoresin (Petition at 5).

The USAN Council's General Rule 4 states, "A name should be free from conflict with other nonproprietary names and with established trademarks and should be neither confusing nor chemically misleading. . . . "

We do not agree that the name zucapsaicin is either confusing or chemically misleading. Zucapsaicin is a geometric isomer of capsaicin – capsaicin is the *trans* (E) isomer and zucapsaicin is the *cis* (Z) isomer. The prefix *zu* serves to differentiate zucapsaicin from capsaicin. Contrary to your request, naming the compound without reference to capsaicin would violate USAN's guiding principles and could be potentially misleading to health care practitioners and the consuming public (see USAN Council's General Rules 3 and 4).[2] In addition, the name you request, civamide, was determined by the USAN Council to conflict with the nonproprietary designations, rifamide, cisapride, cintapride, cinflumide, and cintramide (Petition at Appendix 11, page 4). The USAN Council also determined that there are close to 200 nonproprietrary designations ending in *-amide.* (Petition at Appendix 11, page 4).

To support your claim of confusability, you cite a report you commissioned by Bruce Lambert, Ph.D. of the University of Illinois - Chicago, to assess the comparative confusability of the name zucapsaicin (Petition at 5-7 and Appendix 2). You state that Dr. Lambert developed a computer program that searches databases of drug names to determine similarity in spelling and pronunciation between proposed and existing drug names. For this report, you state that Dr. Lambert conducted several searches of a database of brand and generic names, and you provide the results of one of those searches.

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[2] You cite *GenDerm Corp. v. BioZone Labs.*, Case No. 92C2533, 1992 U.S. Dist. LEXIS 13521 (N.D. Ill. Sept. 3, 1992) to support your position. The court's analysis in this case, however, is not relevant to the comparison of zucapsaicin and capsaicin. This case involved two over-the-counter (OTC) topical analgesic drug products labeled to contain capsaicin as an active ingredient. The defendant's OTC drug product was found to be falsely labeled as it did not contain capsaicin, but contained a compound, identified as "nonivamide," not approved by FDA or listed in the OTC monograph for external analgesic drug products, that was structurally and chemically different from capsaicin. Thus, the court's comparison of these two products in this context is irrelevant to the comparison here of zucapsaicin and capsaicin.

You previously submitted this report to the USAN Review Board. In a letter to the USAN Review Board, the USAN Council reviewed this report (Petition at Appendix 7). Among the methodological problems the USAN Council found with the report was that it did not take into account the USAN Council's use of common stems (similar strings of letters) to identify compounds that belong to the same class based on the compound's mode of action. Thus, all drug products containing the same stem would show up on Dr. Lambert's database as similar, which would be expected, considering the USAN Council's intention of assigning nonproprietary names to identify a compound's relationship to existing classes of compounds (see USAN Council's General Rule 3). The name zucapsaicin was chosen to identify the compound as an isomer of capsaicin. The names have similar letters to intentionally inform health care practitioners that the compound is only different from capsaicin in stereochemistry. The nonproprietary name, zucapsaicin, must relate to capsaicin because it is an isomer of capsaicin.

We do not find Dr. Lambert's report persuasive. In his conclusions Dr. Lambert states, "One factor mitigating against confusion is the fact that the products differ in their initial letters. Similarity in the initial part of words is a very important driving factor in confusions, and if two names have to differ by only two letters, it is best that those differences be at the beginning of the word" (Petition at Appendix 2, page 2). The USAN zucapsaicin identifies the compound as similar to capsaicin in conformity with the USAN Council's guiding principles, and the prefix *zu* serves to differentiate the name, which, according to Dr. Lambert's own conclusions, reduces the risk of confusion. Also, we note that capsaicin is marketed as an over-the-counter (OTC) drug product. As an OTC drug product, no prescription is required for capsaicin's dispensing as would be required if zucapsaicin were approved as a new drug. As Dr. Lambert notes, one of the factors that would affect the rate of confusion of drug products would be whether the product was marketed as a prescription drug product or an OTC drug product (Petition at Appendix 2, page 2). It does not appear that this difference was factored into Dr. Lambert's analysis.[3]

You also suggest that FDA's Phonetic and Orthographic Computer Analysis (POCA) system would be likely to produce similar results to those obtained by Dr. Lambert. FDA's POCA system is designed to evaluate proprietary names, and not nonproprietary names. In his report, Dr. Lambert states that he did not study the brand (proprietary)

[3] In assessing the limitations of his report, Dr. Lambert states, "My research suggests very strongly that, for most types of confusion, the error rate increases as similarity increases. Thus, highly similar pairs of names are more likely to be confused than less similar pairs. The absolute rate of confusion, however, depends upon a wide variety of factors, some of which were not taken into account by this analysis. Among these are prescribing frequency, packaging, storage location, Rx vs. OTC status, the circumstances of use, as well as the mood, experience, and fatigue of the user. In addition, although similarity is a known risk factor for confusion, it is not a perfect predictor. Cigarette smoking is a clear risk factor for lung cancer, but not all cigarette smokers get lung cancer (in fact, only about 10% do). Analogously, not all similar names will be confused, and low similarity does not guarantee against confusion. All one can say with confidence is that, on the whole, similarity tends to increase the risk of confusion. . . ." (Petition at Appendix 2, page 2). These statements indicate many other factors not taken into consideration in the author's assessment of the confusability of the USAN zucapsaicin and your proposed name, civamide.

names of these products (Petition at Appendix 2, page 2). In fact, as zucapsaicin is at the investigational new drug stage of the drug approval process, a proprietary name has not yet been selected for the compound. Thus, your suggestion that the POCA system would likely produce results similar to Dr. Lambert's results is incorrect. In this case, we are in agreement with the USAN Council that the nonproprietary name zucapsaicin is appropriate for the compound.

2. General Rule 5

You state that the name used almost exclusively by the medical and scientific communities for the compound is civamide (Petition at 8). To support your claim, you provide a list of references which, you state, shows that civamide is the de facto name of established usage for the compound.

The USAN Council's General Rule 5 states, "Preference should be given to names of established usage provided they conform to these guiding principles and are determined to be free from conflict with existing nonproprietary names and trademarks."

We note that our regulations at 21 CFR 299.4(d) state, "Prior use of a name in the medical literature or otherwise will not commit the FDA to adopting such terminology as official." Therefore, we are under no obligation to make a decision about the name of a drug product based on prior usage. Furthermore, you raised this issue with the USAN Review Board in 2003, and their review of your claim indicates that no such de facto usage was claimed at the time the USAN Council adopted the USAN in 1993 (Petition at Appendix 11, page 4). The USAN Council states that you and the previous holder continued to use the name civamide after zucapsaicin was adopted as the USAN in 1993 (Petition at Appendix 11, page 4), contrary to both the requirements of the USAN Council and FDA's regulations.

3. Specific Rule 14

You state that the compound is a new chemical entity, is not found in nature and must be chemically synthesized, and that it is not routine under Specific Rule 14 for the stereoisomeric form of a new chemical entity to be identified in the nonproprietary name (Petition at 9). You also state that because the compound is a geometric isomer of capsaicin, it should not be treated as if it were an optical isomer.

The USAN Council's Specific Rule 14 states, in part, "A name coined for a new chemical entity routinely does not specify the stereoisomeric form of the molecule in the nonproprietary name. If the stereochemical configuration has been determined, this information is presented in the chemical name(s) and is reflected in the structural formula. . . . ."

The USAN Council addressed these issues in its June 20, 2003 response (Petition at Appendix 6, page 6). The USAN Council noted that capsaicin is a well-known entity,

existing in nature, which was originally isolated in the 1890's. Zucapsaicin, the chemically synthesized form, was submitted to the USAN Council long after capsaicin was marketed. The USAN Council considers capsaicin to be the new chemical entity and zucapsaicin the new form, so there is no violation of Specific Rule 14. The USAN Council agrees that the compound is a geometric isomer and states that geometric isomers are not specifically listed as examples in the rule because so few have been presented for naming. The USAN Council states that including the existing name in the name of a stereoisomer is necessary in order to correctly identify the compound. Stereoisomers include not only the mirror image enantiomers, but also geometric (cis/trans) isomers and distereoisomers (isomers of drugs with more than one chiral center that are not mirror images of one another).

You cite FDA's Policy Statement for the Development of New Stereoisomeric Drugs (Petition at Appendix 4) to support your claim. We note that this policy statement does not refer to nomenclature issues; it was written to provide guidance on the study and pharmaceutical development of individual enantiomers and racemates as a result of technological advances. FDA regulations acknowledge the USAN Council's expertise in deriving names for drugs (21 CFR 299.4(c)).

We do not agree that the USAN zucapsaicin violates the USAN Council's Specific Rule 14. We have concluded that the use of the prefix *zu* complies with the USAN Council's Specific Rule 14 of the guiding principles. Precedents for using the prefix *zu* to denote *cis* isomers include zuclomiphene and zuclopenthixol. Other prefixes, including *dextro* and *levo*, have been added to existing names to denote the stereoisomers (e.g., dexibuprofen, dexketoprofen, levomenthol, and levonorgestrel). The name you propose, civamide, provides no relationship to its stereoisomer capsaicin.

B. Potential to cause harm

You state that the name zucapsaicin unnecessarily exposes patients, physicians, pharmacists, health care and scientific professionals, and your company to various types of risk, including:

- Potential damage from medication errors arising from confusion between the names zucapsaicin and capsaicin,
- Potential damage to the public from nonuse of zucapsaicin in cases where it would be beneficial,
- Potential damage to any product(s) incorporating zucapsaicin and thereby to your corporation, and
- Confusion within the medical and scientific communities, where civamide is the de facto name of established usage for zucapsaicin.
  (Petition at 4.)

1. Medication errors

From a pharmacist's standpoint, the name zucapsaicin better reflects the characteristics and relationships to capsaicin and is of practical value to health care practitioners (see the USAN Council's General Rule 3, "A name should reflect characteristics and relationships that will be of practical value to the users. . . ."). This relationship is analogous to the common stem names that routinely are incorporated in the names of related drugs with common characteristics. Examples include antihyperlipidemic agents such as lovastatin, pravastatin, atorvastatin, and fluvastatin. You contend that the potency and adverse effects of capsaicin and zucapsaicin differ, and that the similarity in the names of capsaicin and zucapsaicin may cause potential damage from medication errors. FDA disagrees, because not all drugs having the same stem names have the same potency and adverse effects and these differences are addressed in a drug product's labeling (21 U.S.C. 352, 21 C.F.R. 201.56, 201.57).

To support your claim of potential medication errors, you cite a survey of "pain specialists" (defined as physician, pharmacist, or nursing members of the American Pain Society), commissioned by you and conducted by International Research Services, Inc. (IRSI) (Petition at Appendix 5). Of note, the survey states that out of 400 questionnaires sent out by IRSI, only 39 were completed and returned (a response rate of 9.75%) and that only 2 of 3 questions were tabulated (Petition at Appendix 5, page 1). We have reviewed the USAN Council's analysis of this survey and agree with their conclusions on the methodological problems, scientific inadequacy, and serious flaws in the design of the survey (Petition at Appendix 7, page 2). We agree with the USAN Council that the small sample size and low response rate indicates that there is not a proper basis for generalizing the results to all health care practitioners in the United States. We also agree that there is evidence of bias in the introduction to the survey and in the question design (Petition at Appendix 7, page 2). Therefore, we do not find this survey persuasive in supporting your claim that the name zucapsaicin will lead to medication errors.

2. Damage from non-use and damage to future products

You state that there is a potential problem of nonuse arising from the drug name chosen, as patients would be deprived of the positive benefits of the compound because (1) the side effects of capsaicin might be mistakenly attributed to the compound so that physicians might not prescribe it and consumers might not use it, or (2) some physicians and patients may not have experienced efficacious use of capsaicin for its indications and might not be willing to try a similar-sounding compound. You also state that any nonuse could materially damage any future products you might introduce incorporating the compound.

We find these claims to be speculative and without evidence to support them. The labeling and marketing of any future products containing zucapsaicin should address all approved indications and potential side effects of your product. Contrary to your

viewpoint, and for the reasons given above in Section II.A, we believe potential prescribers and users will be able to distinguish zucapsaicin from other marketed drug products.

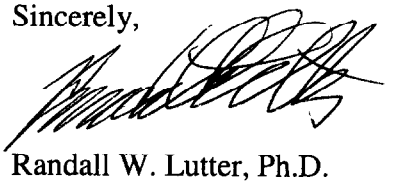
3. Confusion within the medical and scientific community

Lastly, you again raise the issue of confusion within the medical and scientific communities where you state civamide is the de facto name of established usage for the compound. We have addressed this issue in the discussion of the USAN Council's General Rule 5 above. We do not agree that the evidence you present warrants changing the USAN from zucapsaicin to civamide or any other name. The USAN zucapsaicin was adopted over 10 years ago in compliance with the USAN Council's guiding principles. The USAN Council is the recognized body within the United States with expertise in assigning nonproprietary names to meet the stated goals of producing useful and simple nonproprietary names. Changing a nonproprietary name in usage worldwide for more than a decade would likely contribute to, not resolve, any confusion within the scientific and medical communities.

III. CONCLUSION

Your request that FDA designate an official name for the compound different from the current official USAN is denied. We have determined that the USAN zucapsaicin is not unduly complex or lacking utility for any other reason (21 CFR 299.4 (e)). Furthermore the name zucapsaicin does not violate the USAN Council's guiding principles. The USAN zucapsaicin clearly identifies the compound as an isomer of capsaicin and has been the official USAN used in the United States and internationally for over a decade. Therefore, for the reasons discussed above, your petition is denied.

Sincerely,



Randall W. Lutter, Ph.D.
Acting Associate Commissioner
for Policy and Planning